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COMPUTER GRAPHICS AND THE GENERATION OF DNA CONFORMATIONS FOR INTERCALATION STUDIES[†]

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Abstract--We report a series of structures for double-stranded DNA that is in the process of opening up to admit an intercalating drug such as ethidium. Using the method of damped least-squares (suggested by Vitek) to provide ring closure across the base pairs, we obtained backbone conformations for parallel base planes at various specified separations. Conformational energies were then calculated, taking into account solution effects, and the minimum energy was chosen. The resulting conformations can be viewed on an interactive display or drawn with high precision as simulated CPK models in color, with shading and highlights.

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1. INTRODUCTION

There has been considerable interest in the structure of DNA complexed with intercalating drugs, such as ethidium, that may act as mutagens, carcinogens, or chemotherapeutic agents. The goal of the present work was to produce a possible model for "opened" double-stranded DNA that could be used to study DNA interactions with various intercalating drugs. The plan was to generate a fragment of six base pairs, with the two center base planes separated by a specified distance d. For six values of d in the interval from 3.38 Å to 6.76 Å, a minimum energy conformation was found, assuming the opening was filled by the water solvent rather than by any drug molecule. The interaction of various drugs with these opened conformations is now being simulated and will be reported later.

Alden and Arnot (1975) constructed similar models, using constraints like those discussed here, but simpler energy functions. Sobell and his group (Tsai et al., 1977; Jain et al., 1977; Sobell et al., 1977) at the University of Rochester made X-ray studies of many crystals of dinucleotides combined with intercalating agents and have proposed a standard form of opened DNA consistent with these studies. The only energy considerations involved were hard-sphere steric repulsions of the CPK† models used as the first step in obtaining the coordinates for these stereochemically limited structures.

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†Reference to a company or product name does not imply approval or recommendation of the product by the University of California or the U.S. Department of Energy to the exclusion of others that may be suitable.

In the present work, we make some simplifying assumptions to narrow down the search space of possible DNA double-helical conformations, but we use much more sophisticated energy calculations. In Section 2, we discuss in detail the geometric assumptions G0 through G5, and the energetic assumptions E1 through E3. Next, we describe in Section 3 the process of generating the conformations, and in Section 4, the method of computing their energies. The results are presented in Figs. 6 and 7. These figures were produced by a novel computer-graphics program, which is described briefly in Section 5.

2. THE GEOMETRICAL AND ENERGETIC ASSUMPTIONS

A six-base-pair fragment of double-stranded DNA was considered large enough for studying the DNA interaction with small drug molecules. Figure 1 shows these six base pairs, the center two having a more than normal separation. The geometrical assumptions are as follows:

G0. All bond lengths, bond angles, and hydrogen bonds are fixed, according to the data in Arnot et al. (1969) and Arnot et al. (1976). Only torsion angles are free to vary.

G1. The rings of both bases in a base pair lie in a common plane.

G2. Successive base pairs lie in parallel planes, which are therefore perpendicular to the helix axis. The two center planes are separated by a distance d, and all others are separated by 3.38 Å.

G3. There is an axis of two-fold rotation symmetry between the two center base pairs.

G4. The sugar conformations are fixed either both in a C2'-endo pucker, as determined in Arnot et al. (1976), or in alternating C3'-endo and C2'-endo puckers, as suggested by Sobell et al. (1977).

In the B form of DNA (Arnot et al., 1976), the bases are neither quite perpendicular to the helix axis nor are they exactly coplanar. Therefore, as a starting point, a "pseudo B" conformation was created by the methods described in Section 3. It closely approximates the B form. We then assume that both the top two and bottom two base pairs are in this form, as stated in G5.

G5. All torsion angles agree with those of the pseudo B form except for the glycosidic C-N bonds of the two center base pairs and for the sugar-phosphate backbones connecting the two center base pairs to each other and to adjacent bases.

Assumptions G0, G4, and G5 limit the number of free variables to four glycosidic angles and 30 sugar-phosphate backbone torsion angles. These are equal in pairs, related by the symmetry of assumption G3, so it remains to determine 17 torsion angles.

As explained in Section 3, the addition of assumptions G1 and G2 to those already discussed above reduces the number of degrees of freedom among the 17 variables to four. This gives too large a search space in which to locate energy minima. Therefore, a further energetic assumption is made:

E1. The minimum energy conformation for a fixed d is also a minimum for the subconformations obtained by considering only the two center base pairs and their connecting backbone.

This separates the search into a three-dimensional search followed by a one-dimensional scan. Because it would be impractical to repeat the analysis for every possible sequence of bases, we additionally assume E2.

E2. The minimum energy conformation is independent of the base sequence.

There is some evidence (Pack and Loew, 1978) that base pair specificity for ethidium intercalation may result from differences in the steric energy required to open up the bases. We have carried out the analysis with the two

center base pairs (the only two that should significantly affect this steric energy) being 3'G-A5' and 3'T-C5'. Hence our analysis is correct for this specific sequence. In studying sequence-specific interactions with various drugs, we intend initially to substitute bases without changing the sugar-phosphate backbone conformation and later to repeat the whole analysis.

In computing the interaction of a drug with DNA, we must also limit the size of the search space. Thus, we impose the additional constraint:

E3. The conformation of DNA for the minimum joint energy of DNA with an intercalating drug can be found by minimizing the energy of DNA alone in the water solvent, subject to the artificial constraint of a 6.76-Å base-plane separation. (This conformation may not be a thermodynamic energy minimum for DNA alone.)

3. GENERATING CONFORMATIONS

By assumption E1, it is sufficient to first find a minimum-energy conformation for the two center base pairs. Then we can add the backbone for the transition between these and pseudo-B form and minimize its energy, subject to the constraint of consistency with the previously found center and pseudo-B glycosidic torsion angles.

We first consider the center two base pairs, as shown in Fig. 2. If the lower base pair lies in the plane $Z = 0$, then the upper base pair lies in the plane $Z = d$. The axis EF of two-fold rotational symmetry of assumption G3 can be taken to be the line $X = 0$, $Z = d/2$, parallel to the Y axis.

By assumptions G0 and G1 each base pair can be treated as a rigid body. In Fig. 2, the two glycosidic bonds for each base in a pair have been extended to meet in their common plane in fake atoms Q and R. The position and orientation of the triangle formed by the two extended bonds at Q then specifies the upper base.

Let us now find the number of degrees of freedom of this two-base-pair configuration, subject to the constraints G0 through G5, and elminating the six rigid-body degrees of freedom of the structure as a whole. As a separate rigid body, the upper base pair has three degrees of freedom of motion in its plane Z = d, one of rotation and two of translation. If this base pair is translated a distance s along the X axis, the two-fold rotational symmetry about EF can be preserved by translating the lower one by minus s along the X axis. Similarly, if the upper base pair is rotated an angle θ about an axis parallel to the Z axis, the lower base pair may be rotated by minus θ about the reflection of this axis in the plane X = 0. However, if the upper base pair is translated along the Y axis, the lower base pair also must be translated, which results in a rigid-body motion of the whole configuration. Thus, the upper base has two degrees of freedom in its motion with respect to the lower base.

There are seven free torsion angles along the backbones connecting the two base planes, two glycosidic angles χ' and χ'', and five sugar-phosphate angles ξ, θ, ψ, ϕ, and ω, as shown in Fig. 2. The backbone edges not labeled with torsion angles in this figure belong to the sugars, which are assumed to keep a fixed pucker.

To match with a fixed position of the bases in the upper and lower planes, a backbone chain starting at the lower base must match up to the fixed triangle at Q when it reaches the upper plane. Because this rigid triangle has six degrees of freedom in space, this matching imposes six constraints. Thus, any one of the seven torsion angles, say ϕ, can be specified in

advance, and there will be at most a finite number of solutions for the other angles. The choice of ϕ is the third degree of freedom for the two-base-pair configuration.

Go and Scheraga (1970) show that when ϕ and the positions of the bases are specified, there are, at most, four solutions for the other six torsion angles, and they give a method for finding them. Instead of using this method, we chose a different approach, which will apply as well to the problem of finding the transition backbone between the two center base pairs and the pseudo B form. For this latter problem, with its peculiar constraints, the method of Go and Scheraga does not apply.

The method of damped least squares was first suggested by Vitek (1968) for the problem of ring closure, which was also handled by Go and Scheraga (1970), but it is in fact more general and can be applied to any system with constraints, even when the constraint equations are not independent.

For the problem of the two center base pairs, consider the chain of 27 atoms shown in Fig. 3. The chain starts with the three atoms C_1, R_2, and C_3 determining the lower base plane and ends with second copies, C_{25}, R_{26}, and C_{27}, of these same three atoms. Assume the first three atoms are at fixed locations in the plane Z = 0. Then any specification for the seven free torsion angles will give a unique position for the whole chain. The constraint of ring closure can be satisfied by requiring that the X, Y, and Z coordinates of C_1 agree with those of C_{25}, and similarly for R_2 with R_{26}, and C_3 with C_{27}. By concatenating appropriate translations and rotations (Vitek, 1968), the coordinates for C_{25}, R_{26}, and C_{27} can be computed in terms of the seven angles χ', χ'', ξ, θ, ψ, ϕ, and ω. The constraints for ring closure are then given by the equations:

$$X_{25} - X_1 = 0$$
$$Y_{25} - Y_1 = 0$$
$$Z_{25} - Z_1 = 0$$
$$X_{26} - X_2 = 0$$
$$Y_{26} - Y_2 = 0$$
$$Z_{26} - Z_2 = 0$$
$$X_{27} - X_3 = 0$$
$$Y_{27} - Y_3 = 0$$
$$Z_{27} - Z_3 = 0 \quad . \qquad (1)$$

These nine equations represent only six independent constraints, since the rigid triangle $C_{25}R_{26}C_{27}$ has only six degrees of freedom. However, no six equations from among the nine above will suffice.

Note that the lengths of the three sides of the triangle $C_{25}R_{26}C_{27}$ already agree with the corresponding lengths in triangle $C_1R_2C_3$ for any conformation generated from the specified bond lengths and bond angles. This is another way to explain why the system in (1) is three-fold over-determined.

Go and Scheraga (1970) proceed to find an equivalent system of six independent analytic equations, necessarily more complicated than the equations in (1). Instead, Vitek (1968) proposes to minimize the sum of the squares of the left-hand sides of these equations, as a function of six of the seven angles. When a solution of (1) exists, the minimum value is 0, and the method of damped least-squares converges to a solution of (1).

If we now add the additional constraint G2, we get three more equations by requiring that C_{13}, Q_{14} and C_{15} lie in the plane Z = d:

$$Z_{13} - d = 0$$
$$Z_{14} - d = 0$$
$$Z_{15} - d = 0 \quad . \qquad (2)$$

Equations (1) and (2) represent our geometrical assumptions, G0 through G5, in a system of 12 equations in seven unknowns. At first glance, one would expect no solutions at all. However, we have seen that the space of conformations satisfying these constraints actually has three degrees of freedom: two for the position of the upper base pair with respect to the lower and one more for the backbone connecting them. Therefore, any three of the angles may be specified, and a finite number of solutions may still be expected.

The sum of the squares of the left hand sides of (1) and (2) is minimized as a function of the four free angles. In an appropriate range of values of d and the three fixed angles, a minimum of 0 can be obtained, which gives a solution to (1) and (2).

These solution conformations were generated and reviewed on the Evans and Sutherland (E&S) "Case Shaded Graphics System" at Case Western Reserve University, which can produce line drawings like the one in Fig. 3, as well as shaded raster drawings. The rotations and translations generating the chain of atoms from the bond lengths and angles were represented as 4 x 4 matrices (Newman and Sproull, 1979), which could be concatenated very efficiently in the E&S pipelined hardware.

Specifically, let the bond from atom k-1 to atom k have length d_k, let the bond angle at atom k be θ_k, and let the torsion angle between the plane containing atoms k-2, k-1, and k and the plane containing atoms k-1, k, and k+1, be τ_k. (When k = 1, let θ_k and τ_k be 0, and when k = 2, let τ_k = 0.)

Because of the available software and hardware, we define the transformation matrices following the conventions of Newman and Sproull (1979) and Jones (1976) rather than Vitek (1968). Let A_k be the 4 x 4 matrix:

$$A_k = \begin{vmatrix} \cos\theta_k & -\sin\theta_k \cos\tau_k & \sin\theta_k \sin\tau_k & 0 \\ \sin\theta_k & \cos\theta_k \cos\tau_k & -\cos\theta_k \sin\tau_k & 0 \\ 0 & \sin\tau_k & \cos\tau_k & 0 \\ d_k & 0 & 0 & 1 \end{vmatrix}$$

Let $B_n = \prod_{k=n}^{1} A_k = A_n A_{n-1} \ldots A_1$. (The product B is written in the reversed order, since the matrices A_k are the transposes of the usual ones.) If e is the row vector (0, 0, 0, 1), then eB_n is the row vector $P_n = (X_n, Y_n, Z_n, 1)$, giving the coordinates of the nth atom.

In our case, all the d_k's, and θ_k's and all but four of the τ_k's are fixed, and, because of our geometrical assumptions, $A_{k+11} = A_k$.

The partial derivative vector,

$$\frac{\partial P_n}{\partial \tau_k} = \left(\frac{\partial X_n}{\partial \tau_k} , \frac{\partial Y_n}{\partial \tau_k} , \frac{\partial Z_n}{\partial \tau_k} , 0 \right)$$

can thus be computed as

$$\frac{\partial P_n}{\partial \tau_k} = \begin{cases} 0, & n < k ; \\ e \left(\prod_{i=n}^{k+1} A_i \right) \frac{\partial A_k}{\partial \tau_k} \left(\prod_{i=k-1}^{1} A_i \right) , & k \leq n < k + 11 ; \\ e \left[\left(\prod_{i=n}^{k+1} A_i \right) \frac{\partial A_k}{\partial \tau_k} \left(\prod_{i=k-1}^{1} A_i \right) \right. & \\ \qquad \left. + \left(\prod_{i=n}^{k+12} A_i \right) \frac{\partial A_k}{\partial \tau_k} \left(\prod_{i=k+10}^{1} A_i \right) \right] , & n \geq k + 11 . \end{cases} \tag{3}$$

(In these equations, an empty product $\prod_{i=j}^{k}$ for which no i is between j and k, is assumed to equal the identity matrix.)

The matrices A_k and their partial derivatives are conveniently specified in an extension of Algol (Jones, 1976), which takes advantage of the special purpose graphics hardware of the system. They are multiplied together on the hardware 4 x 4 matrix multiplier to determine the coordinates of the atoms and their derivatives. The method of damped least squares is then applied, as described in Vitek (1968).

The computer program allows any of the seven free torsion angles to be initialized, and any selected subset to be kept fixed during the iteration. The solution to which the computation converges depends on these settings. For the first step, all angles were initialized at values computed from the B-form coordinates presented by Arnot et al. (1976). All seven free angles were permitted to vary, and a nearby pseudo B form was found that satisfied our geometric assumptions.

Then the base plane separation d was increased in five small stages, and at each stage, the three angles χ', χ'', and ω were stepped through various values to find the minimum energy. For some values of these fixed parameters, there may be no solution at all to (1) and (2), and the iterations will not converge. The convergence of the sum of the squares towards zero was monitored interactively, and the resulting backbone configurations were reviewed in vector mode on the E&S system, which is capable of rotating them in real time. Calculations that did not converge could be aborted at any point.

Over a hundred conformations were generated in this way, using a previous conformation as a starting point and changing one or more of the fixed parameters slightly. Our analysis of the degrees of freedom indicates that

when three angles are specified, there are at most a finite number of solutions to (1) and (2), and gross changes are needed to move from one solution to another. The damped least-squares calculation will converge to the solution closest to the conformation used as a starting point. For each new larger separation, we search for a constrained energy minimum near the minimum for the previous separation. Thus, our limited search progresses along an energy valley towards the opened form.

Once an optimal conformation for the two center base pairs has been determined for a specific base-plane separation, a similar technique can be used to match it up to the pseudo B form.

In Fig. 4, we show the region between those base pairs that lie second and third from the top in Fig. 1. The two glycosidic angles marked χ are to agree with the pseudo B form, and the two marked χ' and χ'' are to agree with those found from a previous computation for the two opened center base pairs. The angles are no longer equal in pairs, since the axis of symmetry lies below the lower base pair. Therefore, there are ten torsion angles that can vary, marked ξ', θ', ψ', ϕ', ω', ξ'', θ'', ψ'', ϕ'', and ω''.

The nine equations in (1) still represent six independent constraints, and without the presence of the two-fold symmetry, the three equations in (2) represent three more constraints. Therefore, there is one degree of freedom remaining in the system. One of the ten angles can be specified, and the same method of damped least squares is used to solve for the other nine. The energy can then be minimized as a function of the one fixed angle.

Thus, a four-dimensional minimization has been divided into a three-dimensional search, followed by a one-dimensional search. The minimum energy for the configuration for the constant C2'-endo pucker, shown in Figs. 1 and 7, had a total unwinding angle of 6.45 deg when compared to the pseudo-B helix, which rotates 35.53 deg per base.

Once the 27-atom closed cycle has been found, the atomic coordinates for the other atoms in the bases, sugars, and phosphates can be computed similarly as products of matrices A_k, working back to a reference atom among the original 27. Standard files were created for each base, and an arbitrary base sequence could be specified, although only one was actually used.

At this stage, the interactive display of the sort shown in Fig. 2 was used mainly to debug the data files employed in attaching atoms to the backbone. The resulting coordinate file, for all atoms including the hydrogens, was then punched onto paper tape, and read into a disc file on a Univac 1108.

4. ENERGY COMPUTATIONS

The conformational energy of the DNA molecule was evaluated by the Univac 1108, using a molecular mechanics formalism (Warshell et al., 1977). A fixed-valence geometry was assumed in these calculations. Therefore, the conformational energy is only a function of the torsional angles. The calculating system used to evaluate the energy is comprised of subroutines of the CAMSEQ-II molecular mechanics program (Potenzone and Hopfinger, 1977; Hopfinger, 1973). This system was selected because of its success in predicting conformations of various types of molecules including polysaccarides (Potenzone and Hopfinger, 1978), polypeptides (Hopfinger, 1973, and 1977), and drugs (Petit et al., 1979).

A fixed-valence geometry molecular-mechanics formalism assumes that the total potential energy is the sum of the pairwise interactions between all the nonbonded atoms of the molecule. The energy is partitioned into four components (steric, electrostatic, hydrogen bonding, and solvation energies).

Steric energy

This is evaluated by the Lennard-Jones 6-12 potential function,

$$E_{steric} = \sum' \left(\frac{-A_{ij}}{r_{ij}^{6}} + \frac{B_{ij}}{r_{ij}^{12}} \right) ,$$

where A_{ij} and B_{ij} are the attractive and repulsive coefficients, respectively; r_{ij} is the distance between atoms i and j; and the sum $\sum'$ is taken only over nonhydrogen-bonded pairs of atoms that are more than two bonds apart or on different DNA chains.

Electrostatic energy

This energy is calculated by assuming a monopole interaction between the atoms using a Coulomb law potential,

$$E_{electrostatic} = \sum' \frac{K\, Q_i\, Q_j}{E\, r_{ij}} ,$$

where Q_i is the partial charge assigned to atom i, K is a conversion factor, r_{ij} is the distance between atoms i and j, E is the dielectric constant of the medium (assumed to be 3.5, see Hopfinger 1973), and the sum $\sum'$ is the same as in the steric energy term.

The partial atomic charges used were taken from the literature. The charges for the DNA backbone were reported by Olsen and Flory (1972), and the charges for the bases were calculated by Giessener-Prettre and Pullman (1968). We assumed the partial charges to be constant for the various conformations of the DNA molecule.

Hydrogen-bonding energy

We used a modified corrected-sum hydrogen-bond function (Hopfinger, 1973; Potenzone, 1978) to calculate this energy. This is a combination of a Lennard-Jones type potential, an electrostatic potential, and correction factors involving both distances and angles:

$$E_{H\text{-bond}} = G \sum'' \left(\frac{-A_{ij}}{(XF(\theta) + r_{ij})^6} + \frac{B_{ij}}{(XF(\theta) + r_{ij})^{14}} + \frac{K\, Q_i\, Q_j}{E\, r_{ij}} \right).$$

Here X and G are correction factors to make the interaction of the optimum hydrogen bond (Hopfinger, 1973) (θ = 180° and D_H = 0.18 nm in Fig. 5) equal to -3.5 kcal/mole, and $F(\theta)$ is the correction factor for the dependence on the bond angle θ:

$F(\theta) = \cos^4(2\theta)$, if $135° \leq \theta \leq 180°$;

$F(\theta) = 0$, if $0 \leq \theta < 135°$.

The rest of the variables are as defined above and the sum $\sum''$ is over all hydrogen-bonded pairs of atoms. To insure the atoms do not become closer than the minimum contact distance, the fourteenth power was used to increase the rate at which the repulsive component rises.

Solvation energy

A hydration shell model (Hopfinger, 1973) was employed to calculate this energy component. Basically, each atom or group of atoms is given a solvation-shell radius such that the shell possesses a certain number of solvent molecules. Because there are many solvation groups on a molecule, the various shells may overlap. The volume of overlap represents a volume from which solvent molecules are excluded, and energy is lost or gained by the

system. Hence, by calculating the volume of overlap and estimating the energy required to remove a solvent molecule from the shell, we can predict a solute-solvent energy. An aqueous solvent medium was used in these calculations.

The total intramolecular energy of the DNA molecule is then expressed as

$$E_{total} = E_{steric} + E_{electrostatic} + E_{H\text{-}bond} + E_{solvation} .$$

The absolute magnitude of this energy has no meaning because it is derived from an empirical force field. However, relative differences in energy, as a function of torsion angles, are meaningful. Therefore, it is an appropriate function to minimize in the present analysis.

It is to be stressed that this work lays a basis for actual intermolecular DNA-drug intercalation calculations by defining a set of DNA substrates. The results of these intercalation calculations will be reported later.

5. COMPUTER GRAPHICS

The structural calculations were directed and monitored interactively, using the vector mode of the E&S system. By reasoning similar to that reported earlier (Max, 1973), the present first author concluded that the constrained system discussed above for the two center base pairs had only two degrees of freedom. It was through this interactive monitoring that the third degree of freedom was discovered.

The E&S system is also capable of rendering raster pictures of surfaces defined in terms of polygons and photographing three color separations through appropriate filters. Other systems see Porter ((1978)) and the following are capable of superior quality, but the E&S system does have the unique ability to rotate or deform in real time a black-and-white shaded raster image of a small molecule.

Figure 6, a space-filling representation, shows the open conformation of the six base pairs found by the constrained-energy-minimization calculations described above. Figure 7 shows a ball-and-stick representation of the minimum energy position for ethidium intercalated into this open conformation. These two frames are taken from a 5-minute computer-generated animated movie (Max, 1978) that shows continuous deformations of DNA between the open and closed conformations.

These figures were produced at Lawrence Livermore National Laboratory by a system that treats spheres directly rather than their polyhedral approximations. It evolved from the ATOMS code (Knowlton and Cherry, 1977) written at Bell Telephone Laboratory. ATOMS is capable of computing the visible portions of a scene that consists of interpenetrating spheres and cylinders combined to represent molecular models. It was adapted to run on the CDC 7600 at Livermore by Levine and then further modified by Max (1979a,b) to allow the shading and highlights to be added by the Varian V-75 minicomputer, which controls the Dicomed D-48 color film recorder. Thus, the CDC 7600 need only compute the outlines of the visible portions for each sphere or cylinder, and the location for the highlights, and need not output the millions of intensity values for each frame.

The visible surface computation for Fig. 6 took 2 seconds of CDC 7600 time. Details of the hidden surface algorithm are given by Knowlton and Cherry (1977) and Max (1979a,b).

The Varian-Dicomed system took 100 seconds to record the image shown in Fig. 6 at 2048 x 2048 pixel resolution. The atoms of each color were shaded through the appropriate color of a computer-controlled color-filter wheel, and then the highlights were added through a clear filter. The shading algorithm takes advantage of the Dicomed's color look-up tables to compute the shading or highlight intensities with just two, 30-bit, integer additions per pixel. Details can be found in papers by Max (1979a,b).

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DB/bg

FIGURE CAPTIONS

Fig. 1 Computer-generated drawing of six base pairs of DNA with two center pairs opened.

Fig. 2 Computer-generated drawing of the two center base pairs, showing seven free torsion angles.

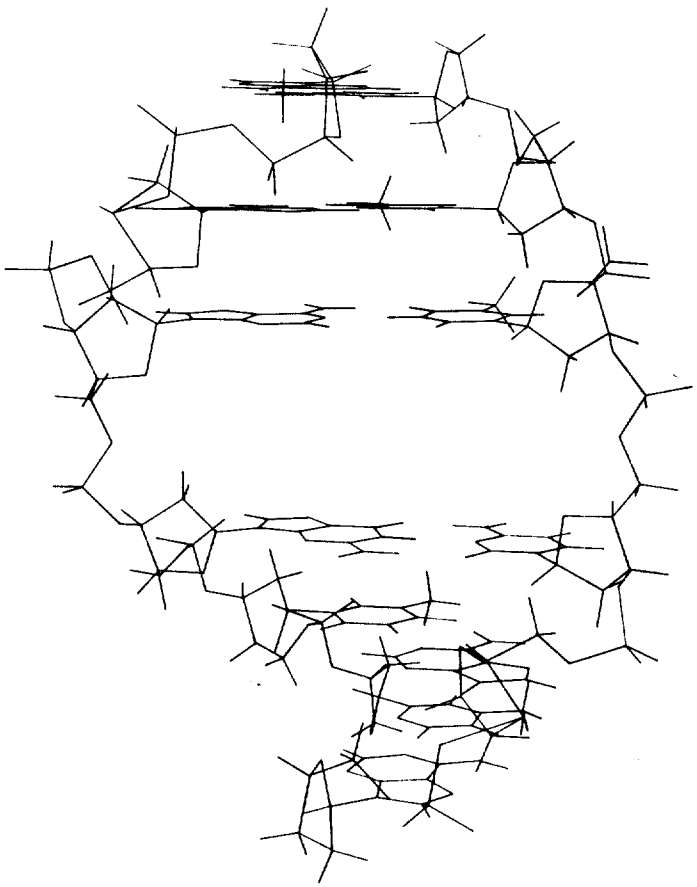
Fig. 3 Drawing of twenty-seven atom chain to be closed into a cycle.

Fig. 4 Drawing of two transition base pairs. Lower pair is to match with that in Fig. 2, and upper pair is to match with pseudo B form.

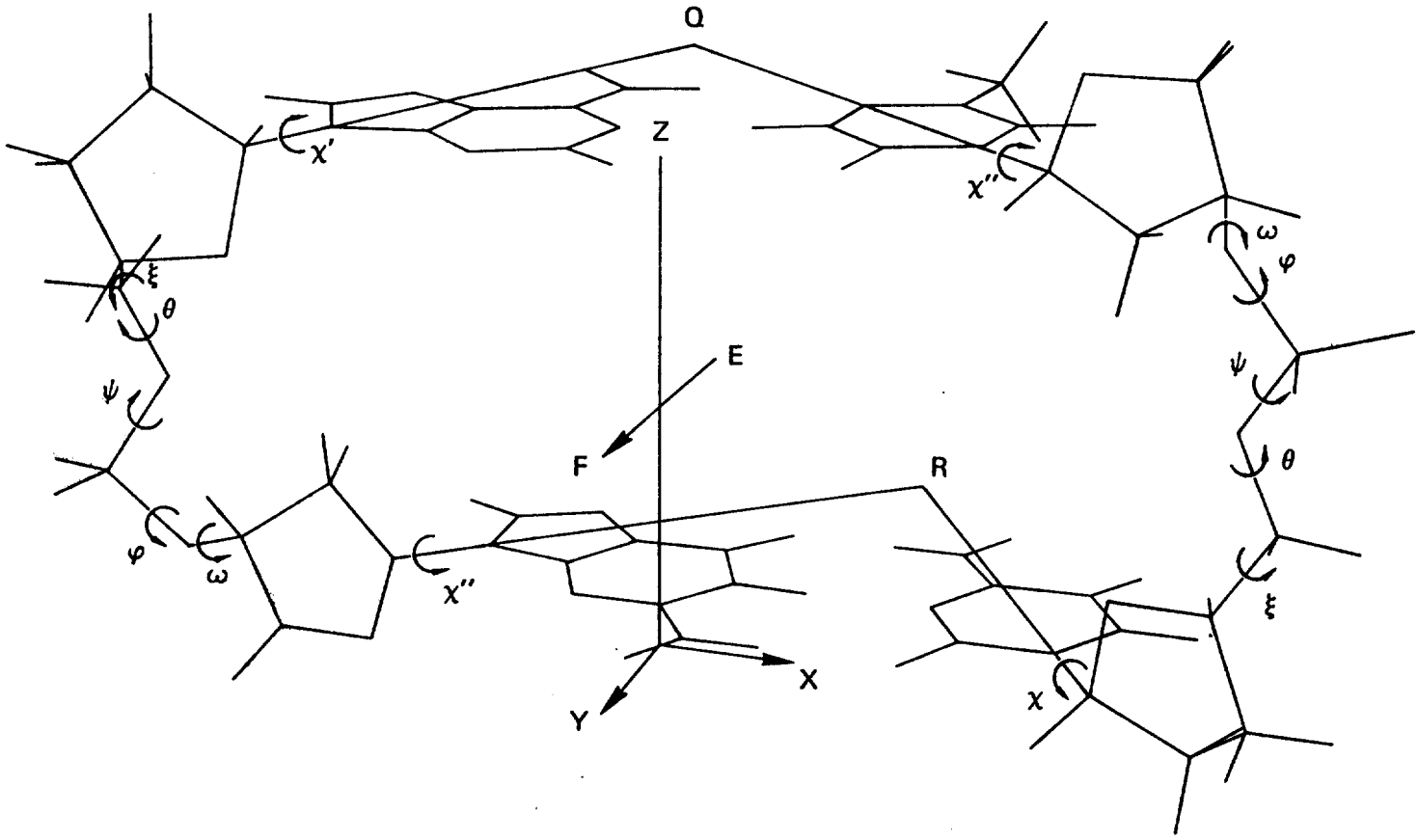
Fig. 5 Hydrogen-bond geometry, D being the donor atom (N or O) and A being the acceptor atom (N or O).

Fig. 6 Space-filling representation of six base pairs of DNA with two center pairs opened.

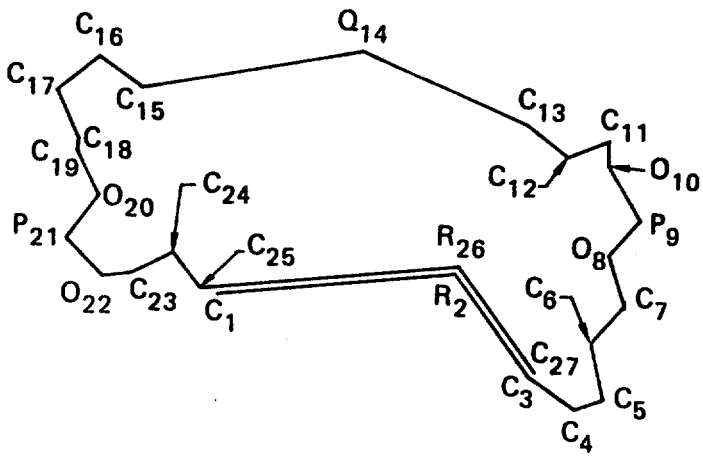
Fig. 7 Ball-and-stick representation of six base pairs of DNA with intercalated ethidium.



Max - Fig. 1



Max - Fig. 2


C16
Q14
C17
C15
C13
C11
C18
C19
C12
O10
O20
C24
P21
P9
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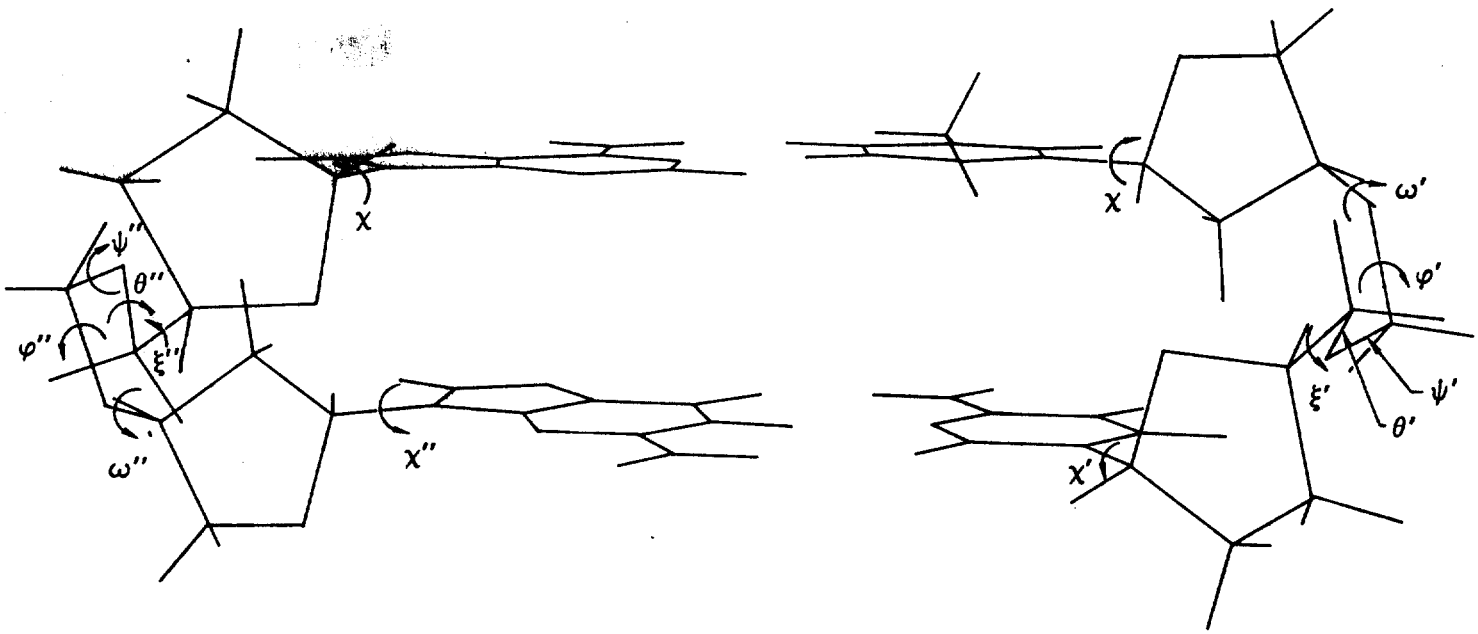
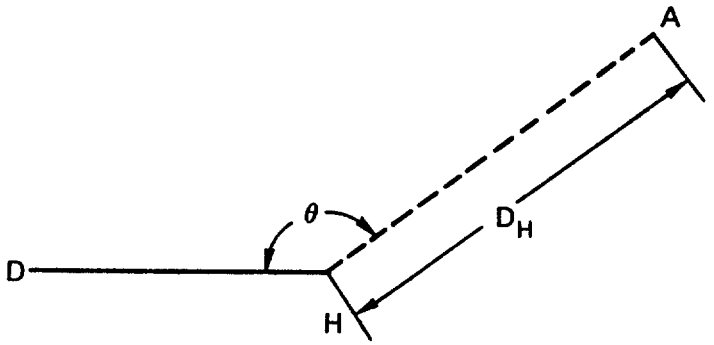
R26
O8
O22
C23
C1
R2
C6
C7
C27
C3
C5
C4

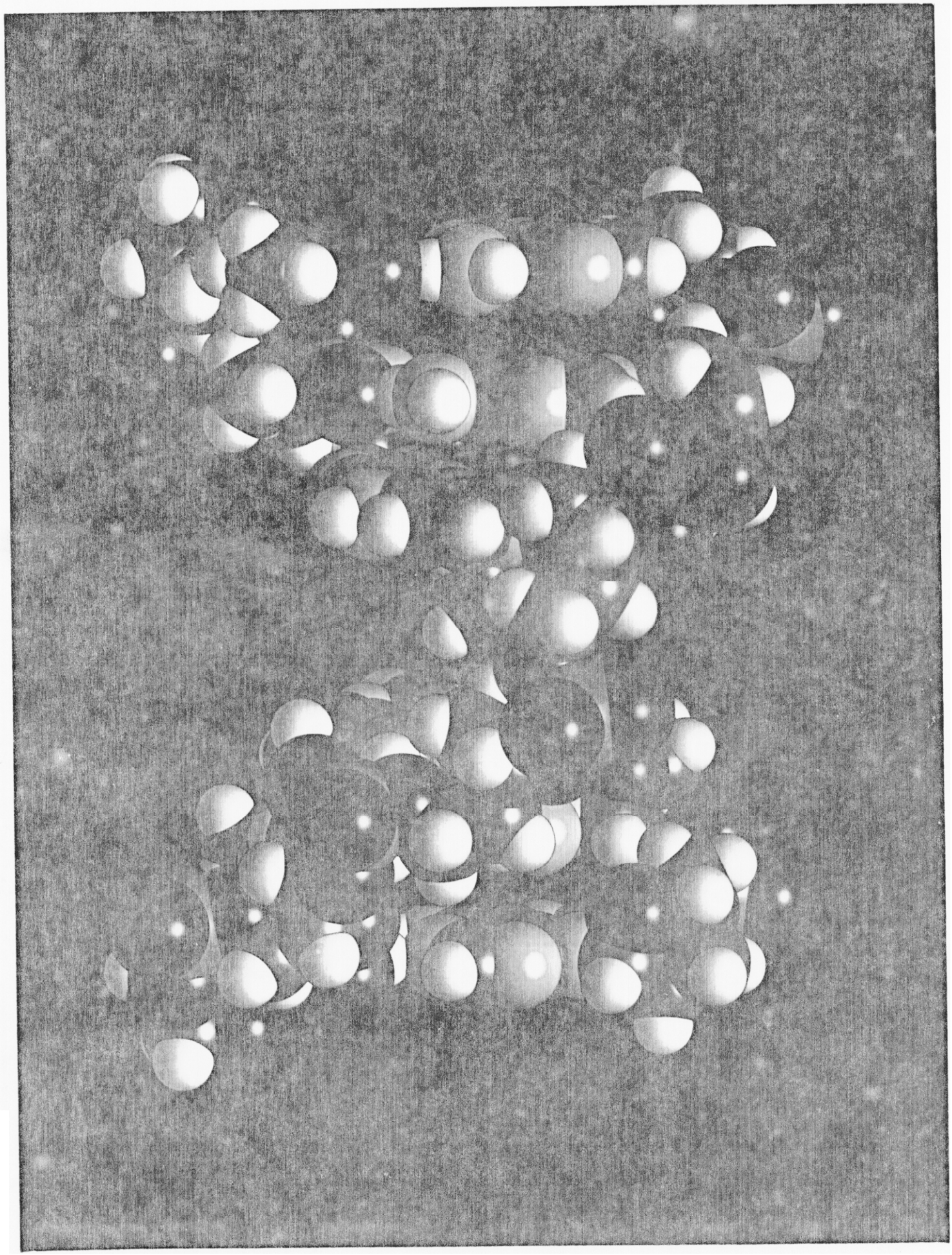
Max - Fig. 3



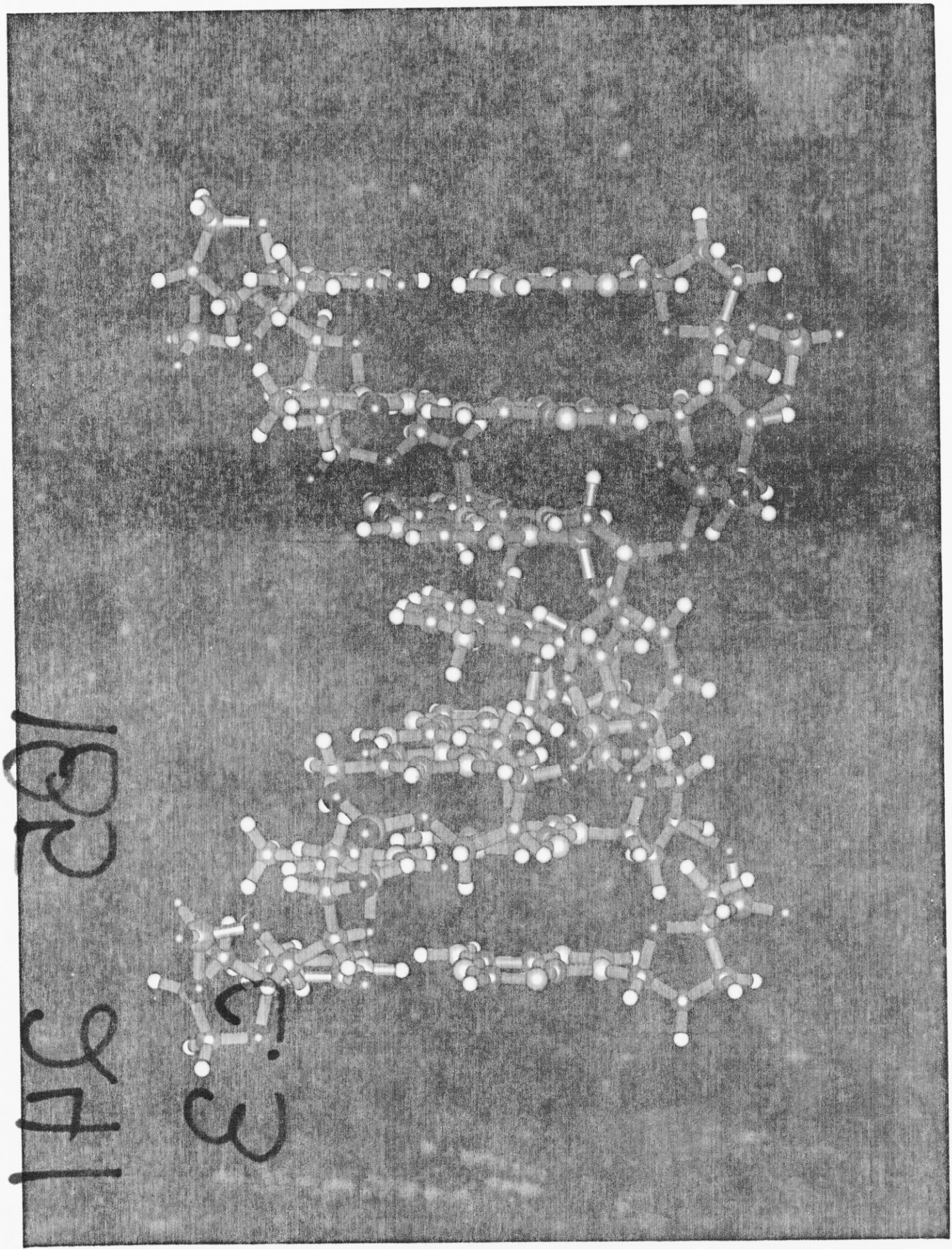
Max - Fig. 4



Max - Fig. 5



Max - Fig. 6



Max - Fig. 7